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=> s "I-FLICE-2"
L1             3 "I-FLICE-2"

=> dup remove l1
PROCESSING COMPLETED FOR L1
L2             3 DUP REMOVE L1 (0 DUPLICATES REMOVED)

=> d l2 1-3 cbib abs

L2   ANSWER 1 OF 3  BIOSIS  COPYRIGHT (c) 2004 The Thomson Corporation.  on STN
2004:111285  Document No.: PREV200400114842. I-FLICE, a novel inhibitor of
     tumor necrosis factor receptor-1 and CD-95 induced apoptosis. Ni, Jian
     [Inventor, Reprint Author]; Rosen, Craig A. [Inventor]; Dixit, Vishva M.
     [Inventor]; Gentz, Reiner L. [Inventor]; Kenny, Joseph J. [Inventor].
     ASSIGNEE: Human Genome Sciences, Inc.; The Regents of the University of
     Michigan. Patent Info.: US 6680171 January 20, 2004. Official Gazette of
     the United States Patent and Trademark Office Patents, (Jan 20 2004) Vol.
     1278, No. 3. http://www.uspto.gov/web/menu/patdata.html. e-file.
     ISSN: 0098-1133 (ISSN print). Language: English.
AB   The present invention relates to a novel I-FLICE-1 or I-
     FLICE-2 protein which is a novel inhibitor of INFR-1 and
     CD-95 induced apoptosis.  In particular, isolated nucleic acid molecules
     are provided encoding the human I-FLICE-1 or I-FLICE-
     2 protein.  I-FLICE-1 or I-FLICE-2
     polypeptides are also provided as are vectors, host cells and recombinant
     methods for producing the same.  The invention further relates to
     screening methods for identifying agonists and antagonists of I-FLICE-1 or
     I-FLICE-2 activity.  Also provided are
     therapeutic methods for treating diseases and disorders associated with
     apoptosis.

L2   ANSWER 2 OF 3  BIOSIS  COPYRIGHT (c) 2004 The Thomson Corporation.  on STN
2003:485623  Document No.: PREV200300485623. I-flice, a novel inhibitor of
     tumor necrosis factor receptor-1 and CD-95 induced apoptosis. Ni, Jian
     [Inventor, Reprint Author]; Rosen, Craig A. [Inventor]; Dixit, Vishva M.
     [Inventor]; Gentz, Reiner L. [Inventor]; Kenny, Joseph J. [Inventor].
     ASSIGNEE: Human Genome Sciences, Inc.; The Regents of the University of
     Michigan. Patent Info.: US 6623938 September 23, 2003. Official Gazette of
     the United States Patent and Trademark Office Patents, (Sep 23 2003) Vol.
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1274, No. 4. http://www.uspto.gov/web/menu/patdata.html. e-file.
ISSN: 0098-1133 (ISSN print). Language: English.

AB The present invention relates to a novel I-FLICE-1 or **I-FLICE-2** protein which is a novel inhibitor of TNFR-1 and CD-95 induced apoptosis. In particular, isolated nucleic acid molecules are provided encoding the human I-FLICE-1 or **I-FLICE-2** protein. I-FLICE-1 or **I-FLICE-2** polypeptides are also provided as are vectors, host cells and recombinant methods for producing the same. The invention further relates to screening methods for identifying agonists and antagonists of I-FLICE-1 or **I-FLICE-2** activity. Also provided are therapeutic methods for treating diseases and disorders associated with apoptosis.

L2 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2004 ACS on STN

1998:509282 Document No. 129:132226 Cloning and cDNA sequence of human I-FLICE inhibitor of tumor necrosis factor receptor-1 and CD-95 induced apoptosis. Ni, Jian; Rosen, Craig A.; Dixit, Vishva M.; Gentz, Reiner L.; Kenny, Joseph J. (Human Genome Sciences, Inc., USA; The Regents of the University of Michigan). PCT Int. Appl. WO 9831801 A1 19980723, 119 pp. DESIGNATED STATES: W: CA, JP; RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1998-US969 19980121. PRIORITY: US 1997-34205 19970121; US 1997-54800 19970805.

AB The present invention relates to a novel I-FLICE-1 or **I-FLICE-2** protein which is a novel inhibitor of tumor necrosis factor receptor-1 and CD-95 induced apoptosis. In particular, cDNA mols. encoding the human I-FLICE-1 or **I-FLICE-2** protein were isolated from human umbilical vein endothelial cell cDNA libraries. I-FLICE-1 cDNA contains an open reading frame for a 480-amino acid residue protein, and **I-FLICE-2** cDNA encodes a 358-amino acid protein. I-FLICE-1 was also identified in cDNA libraries from smooth muscle, and **I-FLICE-2** cDNA was identified in the cerebellum. I-FLICE-1 binds to FLICE proteinase and Mch4/FLICE2, and its overexpression results in inhibition of cell death induced by tumor necrosis factor receptor-1 or CD-95. I-FLICE-1 or **I-FLICE-2** polypeptides are also provided as are vectors, host cells and recombinant methods for producing the same. The invention further relates to screening methods for identifying agonists and antagonists of I-FLICE-1 or **I-FLICE-2** activity. Also provided are therapeutic methods for treating diseases and disorders associated with apoptosis.

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=> s I-FLICE?
L3          55 I-FLICE?

=> dup remove l3
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L4          34 DUP REMOVE L3 (21 DUPLICATES REMOVED)

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L4 ANSWER 1 OF 34 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

2004:111285 Document No.: PREV200400114842. **I-FLICE**, a novel inhibitor of tumor necrosis factor receptor-1 and CD-95 induced apoptosis. Ni, Jian [Inventor, Reprint Author]; Rosen, Craig A. [Inventor]; Dixit, Vishva M. [Inventor]; Gentz, Reiner L. [Inventor]; Kenny, Joseph J. [Inventor]. ASSIGNEE: Human Genome Sciences, Inc.; The Regents of the University of Michigan. Patent Info.: US 6680171 January 20, 2004. Official Gazette of the United States Patent and Trademark Office Patents, (Jan 20 2004) Vol. 1278, No. 3. http://www.uspto.gov/web/menu/patdata.html. e-file. ISSN: 0098-1133 (ISSN print). Language: English.

AB The present invention relates to a novel **I-FLICE**-1 or **I-FLICE**-2 protein which is a novel inhibitor of INFR-1 and CD-95 induced apoptosis. In particular, isolated nucleic acid molecules are provided encoding the human **I-FLICE**-1 or **I-FLICE**-2 protein. **I-FLICE**-1 or **I-FLICE**-2 polypeptides are also provided as are vectors, host cells and recombinant methods for producing the same. The invention further relates to screening methods for identifying agonists and antagonists of **I-FLICE**-1 or **I-FLICE** -2 activity. Also provided are therapeutic methods for treating diseases and disorders associated with apoptosis.

L4 ANSWER 2 OF 34 CAPLUS COPYRIGHT 2004 ACS on STN

2004:515711 Document No. 141:67862 Modulation of stem cell differentiation by modulation of caspase-3 activity and drug screening applications. Megeney, Lynn (Ottawa Health Research Institute, Can.). PCT Int. Appl. WO 2004053144 A2 20040624, 108 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-CA1911 20031210. PRIORITY: US 2002-PV431991 20021210; US 2002-PV431990 20021210.

AB Methods of directing stem cell fate for therapeutic purposes through the deliberate manipulation of caspase-3 activity are provided. The use of modulators of caspase-3 activity to modulate stem cell differentiation is described including activators and/or effectors of caspase-3, which can be used to induce stem cell differentiation, and inhibitors of caspase-3, which can be used to inhibit differentiation and thereby promote or maintain proliferation of stem cells. Methods of screening for modulators of caspase-3 and the use of such compds. to modulate stem cell differentiation in vitro or in vivo are also provided as are therapeutic applications of the compds. Exemplary modulation of differentiation of muscle stem cells (myoblasts) is described. The distribution of pro-caspase 3 and active caspase 3 in myoblasts and in primary striatal stem cells grown under growth conditions and differentiation conditions was examined

L4 ANSWER 3 OF 34 CAPLUS COPYRIGHT 2004 ACS on STN

2004:515644 Document No. 141:65052 Methods for the identification, assessment, and treatment of patients with proteasome inhibition therapy. Mulligan, George; Bryant, Barbara M.; Morrissey, Michael P.; Bolt, Andrew; Damokosh, Andrew I. (Millennium Pharmaceuticals, Inc., USA). PCT Int. Appl. WO 2004053066 A2 20040624, 178 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DE, DK, DK, DM, DZ, EC, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US38539 20031204. PRIORITY: US 2002-PV431514 20021206.

AB The present invention is directed to the identification of markers that can be used to determine whether patients with cancer are clin. responsive or non-responsive to a therapeutic regimen prior to treatment. In particular, the present invention is directed to the use of certain combinations of markers, wherein the expression of the markers correlates with responsiveness or non-responsiveness to a therapeutic regimen comprising proteasome inhibition. Thus, by examining the expression levels of individual markers and those comprising a marker set, it is possible to determine whether a therapeutic agent, or combination of agents, will be most

likely to reduce the growth rate of tumors in a clin. setting.

L4 ANSWER 4 OF 34 CAPLUS COPYRIGHT 2004 ACS on STN
2004:252619 Document No. 140:285716 Identification of sequences particularly useful for the diagnosis and identification of therapeutic targets for osteoarthritis. Marshall, Wayne E.; Liew, Choong-chin; Zhang, Hongwei (Chondrogene Limited, Can.). PCT Int. Appl. WO 2004024892 A2 20040325, 1014 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US29136 20030912. PRIORITY: US 2002-PV410180 20020912.

AB The invention relates to the identification and selection of sequences which demonstrate particular advantage in identifying individuals having osteoarthritis (OA). The invention also provides a selection of sequences particularly useful in diagnosing the degree of advancement of osteoarthritis of an individual and in the identification of novel therapeutic targets for OA. Thus, cDNA libraries were constructed from human fetal, normal, mild, moderate, marked, and/or severe OA cartilage samples. The known and novel clones derived from these libraries were then used to construct human chondrocyte-specific microarrays to generate differential gene expression profiles useful as a diagnostic tools for detection of mild (early stage) OA. Differentially expressed genes are also identified on an Affymetrix Human U133A microarray containing almost 45,000 target sets representing >39,000 transcripts. Arrays of the invention are useful as a gold standard for osteoarthritis diagnosis and for use to identify and monitor therapeutic efficacy of new drug targets. The invention further provides for the use of these sequences as a tool to diagnose disease progression and to monitor the efficacy of therapeutic regimens.

L4 ANSWER 5 OF 34 CAPLUS COPYRIGHT 2004 ACS on STN
2004:85983 Document No. 140:194431 Human prostate cancer marker genes associated with various metastatic stages identified by gene profiling, and related compositions, kits, and methods for diagnosis, prognosis and therapy. Schlegel, Robert; Endege, Wilson O. (Millennium Pharmaceuticals, Inc., USA). U.S. Pat. Appl. Publ. US 2004009481 A1 20040115, 131 pp. (English). CODEN: USXXCO. APPLICATION: US 2002-XA166883 20020611. PRIORITY: US 2001-PV297285 20010611; US 2002-166883 20020611.

AB The invention relates to compns., kits, and methods for diagnosing, staging, prognosing, monitoring and treating human prostate cancers. A variety of marker genes are provided, wherein changes in the levels of expression of one or more of the marker genes is correlated with the presence of prostate cancer. In particular, three sets of the marker genes, corresponding to 11617 GenBank Accession Nos. (only 2168 new submissions) and 15 SEQ IDs, are identified by transcription profiling using RNA derived from clin. samples, that were expressed at least 2-fold or greater than the normal controls. Using TNM staging approach, these markers are divided to three groups, ones can be used to determine whether prostate cancer has metastasized, or is likely to metastasize, to the liver (M stage); ones can be used to determine whether prostate cancer has metastasized, or is likely to metastasize, to the bone (M stage); and ones can be used to determine whether prostate cancer has metastasized, or is likely to metastasize, to the lymph nodes (N stage and/or M stage). The invention also relates to a kit for assessing the specific type of metastatic prostate cancer, e.g., cancer that has metastasized to the liver, bone or lymph nodes. [This abstract record is one of three records for this document necessitated by the large number of index entries required to fully index the document and publication system constraints.].

L4 ANSWER 6 OF 34 CAPLUS COPYRIGHT 2004 ACS on STN
2003:983642 Document No. 140:386189 Molecular mechanisms involved in GnRH analogue-related apoptosis for uterine leiomyomas. Bifulco, G.; Miele, C.; Pellicano, M.; Trencia, A.; Ferraioli, M.; Paturzo, F.; Tommaselli, G. A.; Beguinot, F.; Nappi, C. (Dipartimento di Scienze Ostetrico-Ginecologiche, Urologiche e Medicina della Riproduzione, Naples, 80131, Italy). Molecular Human Reproduction, 10(1), 43-48 (English) 2004. CODEN: MHREFD. ISSN: 1360-9947. Publisher: Oxford University Press.

AB GnRH agonist therapy is known to reduce uterine leiomyoma volume, although the mol. mechanisms responsible for this effect remain poorly understood. In this study, the authors have investigated the mol. mechanisms involved in the anti-proliferative effect of a GnRH agonist, leuprolide acetate (LA), in uterine leiomyomas obtained from 6 patients treated with LA for 3 mo before surgery (group B), compared with tumors from 6 untreated patients (group A). To this end, the authors have evaluated the expression and the activity of mols. involved in the regulation of cell survival and proliferation. In group B, the total activity of PI3K was reduced by 60% compared with control samples. Furthermore, LA caused a reduction of PKB activation of .apprx.50%, measured as serine 473 phosphorylation. In parallel with PKB reduction in LA samples, the authors observed a 60% reduction in the phosphorylation of its substrate BAD. While Bcl-xL/BAD association was not significantly modified in LA-treated leiomyomas, BAD/14.3.3 interaction was reduced, due to a 50% decreased 14.3.3 expression. In addition, LA was able to reduce the expression of the antiapoptotic proteins FLIP and PED/PEA15 by 70 and 50% resp., compared with control samples. The authors next evaluated the activation of MAP kinases in leiomyomas. Activation of p42 and p44 MAP kinase isoforms was increased by 30% in group B. However, the phosphorylation of the transcription factor Elk1 was not increased in a similar fashion in LA-treated leiomyomas compared with group A. Thus, these data suggest that LA reduction of leiomyoma volume is mediated at least in part by a decreased activation of the PI3K/PKB survival pathway and by the suppression of antiapoptotic factors.

L4 ANSWER 7 OF 34 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
2003:485623 Document No.: PREV200300485623. **I-flice**, a novel inhibitor of tumor necrosis factor receptor-1 and CD-95 induced apoptosis. Ni, Jian [Inventor, Reprint Author]; Rosen, Craig A. [Inventor]; Dixit, Vishva M. [Inventor]; Gentz, Reiner L. [Inventor]; Kenny, Joseph J. [Inventor]. ASSIGNEE: Human Genome Sciences, Inc.; The Regents of the University of Michigan. Patent Info.: US 6623938 September 23, 2003. Official Gazette of the United States Patent and Trademark Office Patents, (Sep 23 2003) Vol. 1274, No. 4. http://www.uspto.gov/web/menu/patdata.html. e-file. ISSN: 0098-1133 (ISSN print). Language: English.

AB The present invention relates to a novel **I-FLICE**-1 or **I-FLICE**-2 protein which is a novel inhibitor of TNFR-1 and CD-95 induced apoptosis. In particular, isolated nucleic acid molecules are provided encoding the human **I-FLICE**-1 or **I-FLICE**-2 protein. **I-FLICE**-1 or **I-FLICE**-2 polypeptides are also provided as are vectors, host cells and recombinant methods for producing the same. The invention further relates to screening methods for identifying agonists and antagonists of **I-FLICE**-1 or **I-FLICE** -2 activity. Also provided are therapeutic methods for treating diseases and disorders associated with apoptosis.

L4 ANSWER 8 OF 34 CAPLUS COPYRIGHT 2004 ACS on STN
2003:917753 Document No. 140:40735 Mechanisms of Spontaneous Resolution versus Fibrosis in Granulomatous Experimental Autoimmune Thyroiditis. Chen, Kemin; Wei, Yongzhong; Sharp, Gordon C.; Braley-Mullen, Helen (Departments of. Internal Medicine, University of Missouri School of Medicine, Columbia, MO, 65212, USA). Journal of Immunology, 171(11), 6236-6243 (English) 2003. CODEN: JOIMA3. ISSN: 0022-1767. Publisher:

American Association of Immunologists.

AB When granulomatous exptl. autoimmune thyroiditis (G-EAT) was induced in CBA/J or DBA/1 mice, thyroid lesions resolved in less severe (3+) G-EAT in wild-type mice or severe (5+) G-EAT in IFN-γ-/- mice, but progressed to fibrosis in 5+ G-EAT in wild-type mice. To define the mechanisms leading to these distinct outcomes, the expression of inflammatory and apoptotic mols. and infiltrating cells was evaluated using immunohistochem., RT-PCR, and confocal microscopy. The ratio of CD4+/CD8+ T cells in thyroid infiltrates was one factor that predicted G-EAT outcome. CD4+ T cells outnumbered CD8+ T cells when lesions progressed to fibrosis, while CD8+ T cells outnumbered CD4+ T cells in thyroids that resolved. Fas, Fas ligand, FLIP, TNF-α, inducible NO synthase, TGF-β, and IFN-γ were highly expressed by infiltrating cells when G-EAT progressed to fibrosis. The expression of active caspase-3 was low, possibly contributing to the persistence of CD4+ T cells in fibrosis. In contrast, FLIP was mainly expressed by thymocytes in resolving G-EAT, the expression of active caspase-3 was high, and resolution correlated with apoptosis of infiltrating cells. There was also relatively less expression of TGF-β, IFN-γ, TNF-α, and inducible NO synthase and higher expression of IL-10 in resolving G-EAT than in G-EAT that progressed to fibrosis. These differences were particularly striking when comparing IFN-γ-/- vs wild-type mice. These results suggest that several opposing biol. mechanisms contribute to the outcome of an ongoing autoimmune response. These include differential expression of pro- and antiapoptotic mols., cytokines, and the ratio of CD4+ vs CD8+ T cells.

L4 ANSWER 9 OF 34 MEDLINE on STN DUPLICATE 1

2003352042. PubMed ID: 12649137. Depsipeptide (FR901228) induces histone acetylation and inhibition of histone deacetylase in chronic lymphocytic leukemia cells concurrent with activation of caspase 8-mediated apoptosis and down-regulation of c-FLIP protein. Aron Jennifer L; Parthun Mark R; Marcucci Guido; Kitada Shinichi; Mone Andrew P; Davis Melanie E; Shen Tiansheng; Murphy Timothy; Wickham Joseph; Kanakry Chris; Lucas David M; Reed John C; Grever Michael R; Byrd John C. (Department of Internal Medicine, the Division of Hematology-Oncology, The Ohio State University, Columbus, USA.) Blood, (2003 Jul 15) 102 (2) 652-8. Journal code: 7603509. ISSN: 0006-4971. Pub. country: United States. Language: English.

AB Depsipeptide is in clinical trials for chronic lymphocytic leukemia (CLL) on the basis of earlier observations demonstrating selective in vitro activity in CLL. We sought to determine the relationship of histone H3 and H4 acetylation, inhibition of histone deacetylase, and apoptosis observed in CLL cells to justify a pharmacodynamic end point in these clinical trials. We demonstrate that in vitro depsipeptide induces histone H3 and H4 acetylation and histone deacetylase enzyme inhibition at concentrations corresponding to the LC50 (concentration producing 50% cell death) for cultured CLL cells (0.038 microM depsipeptide). The changes in histone acetylation are lysine specific, involving H4 K5, H4 K12, and H3 K9, and to a lesser extent H4 K8, but not H4 K16 or H3 K14. Depsipeptide-induced apoptosis is caspase dependent, selectively involving the tumor necrosis factor (TNF) receptor (extrinsic pathway) initiating caspase 8 and effector caspase 3. Activation of caspase 8 was accompanied by the down-regulation of cellular FLICE-inhibitory protein (c-FLIP, **I-FLICE**) without evidence of Fas (CD95) up-regulation. Changes in other apoptotic proteins, including Bcl-2, Bax, Mcl-1, and X-linked inhibitor of apoptosis (XIAP), were not observed. Our results demonstrate a relationship between target enzyme inhibition of histone deacetylase, histone H3 and H4 acetylation, and apoptosis involving the TNF-receptor pathway of apoptosis that is not used by other therapeutic agents in CLL. These data suggest use of histone H3 and H4 acetylation, inhibition of histone deacetylase, and down-regulation of FLIP as pharmacodynamic end points for further evaluation of this drug in patients.

L4 ANSWER 10 OF 34 CAPLUS COPYRIGHT 2004 ACS on STN

2003:903679 Document No. 140:57416 Long form of cellular FLICE-inhibitory protein interacts with Daxx and prevents Fas-induced JNK activation. Kim, Young-Youl; Park, Bum-Joon; Seo, Gill-Ju; Lim, Joong-Yeon; Lee, Sang-Min; Kimm, Kyu-Chan; Park, Chan; Kim, Joon; Park, Sang Ick (National Genome Research Institute, National Institute of Health in Korea (KNIH), Eunpyung-Gu, Seoul, 122-701, S. Korea). Biochemical and Biophysical Research Communications, 312(2), 426-433 (English) 2003. CODEN: BBRCA9. ISSN: 0006-291X. Publisher: Elsevier Science.

AB Since Fas-induced apoptosis is major pathway to eliminate unwanted or uncontrolled cells, many types of human cancer cells develop tactful mechanisms to get resistance against the apoptosis. One of the resistant mechanisms in human cancer is overexpression of FLICE-inhibitory protein (c-FLIP), human homolog of viral protein v-FLIP. C-FLIP has multiple splice variants at transcriptional level or two isoforms at protein level, a long (c-FLIPL) and a short form of c-FLIP (c-FLIPS). However, functional differences between these variants are not fully understood. In this study, we show that c-FLIPL but not c-FLIPS phys. binds to Daxx through interaction between C-terminal domain of c-FLIPL and Fas-binding domain of Daxx, an alternative Fas signaling adaptor. Fas-induced cell death and JNK activation are sensitive to Fas stimulation in cell lines carrying undetectable level of c-FLIPL. To support this, overexpression of c-FLIPL but not of c-FLIPS renders the cells resistant to Fas-induced cell death and to JNK activation. In signaling context, the interaction of c-FLIPL with Daxx is likely to inhibit JNK activation by preventing the normal interaction of Daxx and Fas, which is known to lead to apoptosis via JNK activation. This study implies that through this new mechanism, c-FLIPL, acting at both FADD- and Daxx-mediated signaling pathways, may be involved in complete inhibition of Fas-induced cell death and may provide an answer to why c-FLIPL is more abundant and effective than c-FLIPS.

L4 ANSWER 11 OF 34 CAPLUS COPYRIGHT 2004 ACS on STN

2003:401452 Document No. 139:99028 Increased expression of FLIP, an inhibitor of Fas-mediated apoptosis, in stomach cancer. Lee, Sug Hyung; Kim, Hong Sug; Kim, Su Young; Lee, Yun-Sil; Park, Won Sang; Kim, Sang Ho; Lee, Jung Young; Yoo, Nam Jin (Department of Pathology, College of Medicine, The Catholic University of Korea, Seoul, S. Korea). APMIS, 111(2), 309-314 (English) 2003. CODEN: APMSEL. ISSN: 0903-4641. Publisher: Blackwell Munksgaard.

AB Despite the cell surface expression of Fas (Apo-1/CD95), many types of tumor cells, including stomach cancer cells, are resistant to Fas-mediated apoptosis, indicating the presence of inactivating mechanisms of Fas signaling. Expression of FLICE-like inhibitory protein (FLIP), one of the inhibitory proteins of Fas-mediated apoptosis, was reported in several cancer types, but not in stomach cancer. In the present study, the authors analyzed the expression of Fas and FLIP in 60 advanced gastric adenocarcinomas by immunohistochem. using a tissue microarray approach. Immunopositivity (defined as ≥30% of the neoplastic cells) was observed for Fas in 58 (97%) and FLIP in 54 (90%) of the 60 cancers. All of the tumors with FLIP immunostaining also showed Fas immunostaining. Loss of cell surface Fas immunostaining, another mechanism of Fas resistance, was observed in 45 tumors (75%). By contrast, normal gastric mucosal cells showed no or weak expression of both Fas and FLIP. Taken together, these results indicate that increased expression of FLIP is a frequent event in stomach carcinomas, and suggest that for evading apoptosis stomach carcinoma cells in vivo may need FLIP expression, which might contribute to tumor development.

L4 ANSWER 12 OF 34 CAPLUS COPYRIGHT 2004 ACS on STN

2002:970615 Document No. 138:269586 Reactive oxygen species regulate FLICE inhibitory protein (FLIP) and susceptibility to Fas-mediated apoptosis in cardiac myocytes. Nitobe, Joji; Yamaguchi, Seiji; Okuyama, Masaki; Nozaki, Naoki; Sata, Masataka; Miyamoto, Takuya; Takeishi, Yasuchika; Kubota, Isao; Tomoike, Hitonobu (First Department of Internal Medicine, Yamagata University School of Medicine, 2-2-2 Iida-Nishi, Yamagata, 990-9585, Japan). Cardiovascular Research, 57(1), 119-128 (English) 2003.

CODEN: CVREAU. ISSN: 0008-6363. Publisher: Elsevier Science B.V..

AB Objective: Fas ligand (FasL) is a key cytokine which initiates apoptosis when FasL binds to its receptor, Fas. Cardiac myocytes are generally resistant to Fas-induced apoptosis. However, sublethal dose of doxorubicin (Dox) can sensitize cardiac myocytes to Fas-induced apoptosis. We investigated the mol. mechanism by which Dox sensitizes cardiac myocytes to Fas-induced apoptosis. FLICE inhibitory protein (FLIP) is a key mol. for blocking Fas-induced apoptosis by functioning as a caspase-8 dominant neg. Methods and results: FLIP was constitutively expressed in cultured neonatal rat cardiac myocytes. FLIP protein levels were markedly down-regulated by Dox in a time-dependent and dose-dependent manner. Next, we examined the relation of reactive oxygen species (ROS) by Dox to the expression of FLIP. Both of N-acetylcysteine (NAC) and the combination of superoxide dismutase and catalase restored the decreased FLIP in Dox-treated cardiac myocytes to the basal level. NAC also restored the increased formation of thiobarbituric acid-reactive substance after Dox-treatment. Concurrently, the susceptibility to Fas-mediated apoptosis disappeared with the treatments of the antioxidant agents. Hydrogen peroxide down-regulated FLIP in a dose-dependent fashion and also sensitized cardiac myocytes to Fas-induced apoptosis. Conclusions: FLIP, an inhibitor of apoptosis induced by cytokines of TNF family, contributes at least partly to Dox-induced sensitization to Fas-mediated apoptosis in cardiac myocytes. The expression of FLIP in cardiac myocytes is regulated by ROS.

L4 ANSWER 13 OF 34 CAPLUS COPYRIGHT 2004 ACS on STN

2002:798452 Document No. 138:102238 Shiga-Like Toxin Inhibition of FLICE-Like Inhibitory Protein Expression Sensitizes Endothelial Cells to Bacterial Lipopolysaccharide-Induced Apoptosis. Erwert, Ryan D.; Winn, Robert K.; Harlan, John M.; Bannerman, Douglas D. (Department of Medicine, University of Washington School of Medicine, Seattle, WA, 98104, USA). Journal of Biological Chemistry, 277(43), 40567-40574 (English) 2002. CODEN: JBCHA3. ISSN: 0021-9258. Publisher: American Society for Biochemistry and Molecular Biology.

AB Shiga-like toxin (SLT) has been implicated in the pathogenesis of hemolytic uremic syndrome and its attendant endothelial cell (EC) injury. Key serotypes of Escherichia coli produce SLT-1 in addition to another highly pro-inflammatory mol., lipopolysaccharide (LPS). It has previously been established that SLT-1 induces EC apoptosis and that LPS enhances this effect. LPS alone has no affect on human EC viability, and the mechanism for this enhancement remains unknown. In the present report, the authors demonstrate that SLT-1 sensitizes EC to LPS-induced apoptosis. Pretreatment with SLT-1 sensitized EC to LPS-induced apoptosis, whereas pretreatment with LPS did not influence SLT-1-induced apoptosis. SLT-1 exposure resulted in decreased expression of FLICE-like inhibitory protein (FLIP), an anti-apoptotic protein that has previously been shown to block LPS-induced apoptosis. This SLT-1-mediated decrease in FLIP expression preceded the onset of apoptosis elicited by SLT-1 alone or in combination with LPS. SLT-1-mediated decrements in FLIP expression correlated in a dose- and time-dependent manner with sensitization to LPS-induced apoptosis. Finally, transient or stable over-expression of FLIP protected against LPS enhancement of SLT-1-induced apoptosis, and this protection corresponded with sustained expression of FLIP. Together, these data suggest that SLT-1 sensitizes EC to LPS-induced apoptosis by inhibiting FLIP expression.

L4 ANSWER 14 OF 34 CAPLUS COPYRIGHT 2004 ACS on STN

2002:921149 Document No. 138:202566 Loss of expression of death-inducing signaling complex (DISC) components in lung cancer cell lines and the influence of MYC amplification. Shivapurkar, Narayan; Reddy, Jyotsna; Matta, Hittu; Sathyanarayana, Ubaradka G.; Huang, C. X.; Toyooka, Shinichi; Minna, John D.; Chaudhary, Preet M.; Gazdar, Adi F. (Hamon Center for Therapeutic Oncology Research, Dallas, TX, 75390-8593, USA). Oncogene, 21(55), 8510-8514 (English) 2002. CODEN: ONCNES. ISSN: 0950-9232. Publisher: Nature Publishing Group.

AB We have previously reported that the key apoptosis related gene caspase 8 (CASP8) is frequently silenced in small cell lung cancer (SCLC) tumors and cell lines usually, but not always, by aberrant promoter methylation. Because CASP8 is a key component of the death-inducing signaling complex (DISC) when specific death receptors (including DR4, DR5, FAS) are activated by their specific ligands (TRAIL/FASL), we examined expression of the components of the DISC complex in lung cancer cell lines. MYC family members are frequently amplified (MYC+ve) in SCLC, and MYC is a potent inducer of apoptosis. We examined 34 SCLC lines (12 of which were MYC+ve) and 22 NSCLC lines. CASP8 gene expression was frequently lost (79%) at message and protein levels in SCLC but not in non-SCLC (NSCLC). MYC amplification was present in 45% of SCLC cell lines, which had lost CASP8 expression, but not in any of the CASP8 pos. lines. The frequency of CASP8 loss was significantly higher in MYC+ve SCLC compared to MYC-ve SCLC or in NSCLC. Analyses of other DISC components showed significantly higher rates of loss of expression of CASP10, DR5, FAS and FASL in SCLC compared to NSCLC. The loss of expression of proapoptotic DISC components was significantly higher in MYC+ve SCLC cell lines and these lines were completely resistant to TRAIL. Expression of CASP10 (a caspase closely related to CASP8) was frequently absent at the protein level in both SCLC and NSCLC lines. Expression of c-FLIP (proteolytically inactive homolog of CASP8) was inversely related to expression of CASP8. Our major conclusions are: (a) The death receptor pathway is differently inactivated at multiple levels in lung cancer cell lines; and (b) MYC amplification in SCLC is associated with inactivation of most components of the DISC complex, with resistance to TRAIL and with expression of c-FLIP. These findings may have considerable clin. and therapeutic implications.

L4 ANSWER 15 OF 34 CAPLUS COPYRIGHT 2004 ACS on STN
2003:479426 Document No. 140:74828 Influence of HBV infection on TRAIL-induced apoptosis and its mechanism. Han, Lihui; Sun, Wensheng; Ma, Chunhong; Zhang, Lining; Cao, Yinglin; Song, Jing; Chen, Youhai (Department of Microbiology and Immunology, Shandong Medical University, Jinan, 250012, Peop. Rep. China). Zhonghua Yixue Zazhi (Beijing, China), 82(9), 597-600 (Chinese) 2002. CODEN: CHHTAT. ISSN: 0376-2491. Publisher: Zhonghua Yixue Zazhishe.

AB The effect of Hepatitis B virus (HBV) infection on the TRAIL induced apoptosis of the target cells and its mechanism were studied. Two human hepatocellular carcinoma cell lines, HepG2 and its HBV whole genome transgenic cell line named HepG2.2.15, were observed The apoptosis rate of these two cell lines to TRAIL was examined by flow cytometry. The expression of the membrane-bound TRAIL and the secretory soluble TRAIL in the supernatant were assessed by flow cytometry and ELISA, resp. The expressions of the mRNA of TRAIL receptors and FLIP were assessed by semi-quant. PCR. The apoptosis rate of HepG2.2.15 cell line to TRAIL was significantly lower than that of HepG2 cell line (9.12% vs 51.6%, $P < 0.01$). The expression of four TRAIL receptors related to apoptosis was decreased to a more or less degree on HepG2.2.15 cells compared with HepG2 cells, but the expression of FLIP, a protein inhibiting apoptosis at the initial level of the caspase cascade, was drastically upregulated on HepG2.2.15 cells ($P < 0.01$). There was no significant difference in the secretory TRAIL expression between these two cell lines. The results indicated that HBV could make cells resistant to TRAIL-induced apoptosis, this may be realized by the down-regulated expression of TRAIL and its receptors and up-regulated expression of FLIP; and HBV could escape the immune surveillance and persistently existed in the body, which may explain the pathogenesis of HBV related disease in a novel way.

L4 ANSWER 16 OF 34 CAPLUS COPYRIGHT 2004 ACS on STN
2002:235118 Document No. 137:292422 Expression of c-FLIP mRNA in colorectal cancer cells and its relationship with fas antigen (CD95) expression. Gao, Wenchao; Wang, Yuanhe; Li, Li; Wang, Qiang; Zhang, Lingzhen; Cao, Luning; Ding, Erxun (Department of General Surgery, Changzheng Hospital, Second Military Medical University, Shanghai, 200003, Peop. Rep. China). Dier Junyi Daxue Xuebao, 23(1), 35-37 (Chinese) 2002. CODEN: DJXUE5.

ISSN: 0258-879X. Publisher: Dier Junyi Daxue Xuebao Bianjibu.

AB The expression of cellular FLICE-like inhibitory protein (c-FLIP) mRNA in colorectal cancer cells and its relationship with Fas antigen (CD95) expression were studied. RT-PCR was used to detect the expression of c-RLIP mRNA and indirect immunofluorescence label flow cytometry to assay the Fas antigen expression in 3 colorectal cancer cell lines. C-FLIP mRNA was pos. in SW1116 and SW620 cell lines and neg. in LoVo cell lines. The expression of Fas antigen was much higher in SW1116 and SW620 cell lines than that in LoVo cell lines. The expression of c-FLIP mRNA had pos. correlation with the expression of Fas antigen in colorectal cancer cells, and c-FLIP may significantly inhibit the apoptosis induced by Fas in colorectal cancer cells.

L4 ANSWER 17 OF 34 CAPLUS COPYRIGHT 2004 ACS on STN

2001:891252 Document No. 136:32820 Primers for diagnosis and drug screening for autoimmune disease especially for Crohn's disease. Tokunaga, Katsushi; Tsuchiya, Naoyuki (Welfide Corporation, Japan). Jpn. Kokai Tokkyo Koho JP 2001340082 A2 20011211, 14 pp. (Japanese). CODEN: JKXXAF. APPLICATION: JP 2000-162858 20000531.

AB The invention provides primers for human IL-2 regulated protein phosphatase, Traf2 and Nck interacting kinase, FLICE inhibitory protein, glucocorticoid receptor α, cytochrome oxidase subunit I and cytochrome b. The genes encoding these proteins were highly expresses in lesioned part of autoimmune disease especially in Crohn's disease. The primers can be used for diagnosis and drug screening for. Furthermore by the fact that observe to the gene which relates to the disease, can utilize in the screening of the preventive curative medicine of the autoimmune disease and the especially Crohn's disease.

L4 ANSWER 18 OF 34 CAPLUS COPYRIGHT 2004 ACS on STN

2001:593981 Document No. 135:287416 A central role for death receptor-mediated apoptosis in the rejection of tumors by NK cells. Screpanti, Valentina; Wallin, Robert P. A.; Ljunggren, Hans-Gustaf; Grandien, Alf (Department of Immunology, Wenner-Gren Institute, University of Stockholm, Stockholm, S-10691, Swed.). Journal of Immunology, 167(4), 2068-2073 (English) 2001. CODEN: JOIMA3. ISSN: 0022-1767. Publisher: American Association of Immunologists.

AB NK cells provide a line of defense against tumors and virus-infected cells that have lost the expression of one or more MHC class I isoforms. Here, the authors investigate whether inhibitors of apoptosis can block the rejection of tumors mediated by NK cells, by introducing the long form of Fas-associated death domain-like IL-1β-converting enzyme-associated inhibitory protein (FLIPL) and poxvirus cytokine response modifier A (CrmA) into the MHC class I-deficient T lymphoma cell line RMA-S. RMA-S cells do not normally express Fas in vitro, and it was previously postulated that the rejection of these tumors by NK cells is strictly perforin dependent. The authors show that perforin-deficient NK cells directly mediated Fas up-regulation on RMA-S cells and thereafter kill the cells in a Fas-dependent manner, and that RMA-S FLIPL and RMA-S CrmA are protected from such killing. When injected in immunocompetent recipients, RMA-S cells up-regulate Fas, rendering in vivo-passed mock-transduced cells sensitive to Fas-mediated apoptosis. Moreover, RMA-S FLIPL and RMA-S CrmA cells establish aggressive tumors, in contrast to RMA-S mock cells that are rejected. These results demonstrate that FLIPL and CrmA function as tumor progression factors by protecting MHC class I-deficient tumors from rejection mediated by NK cells. Moreover, the authors' data indicate that death receptor-mediated apoptosis has a more prominent role in the clearance of NK-sensitive tumors than previously suggested.

L4 ANSWER 19 OF 34 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

2002:241249 Document No.: PREV200200241249. Cellular adhesion inhibits CD95/Fas-mediated apoptosis by altering the intracellular localization and availability of c-FLIPL. Shain, Kenneth H. [Reprint author]; Landowski, Terry H. [Reprint author]; Dalton, William S. [Reprint author].

Interdisciplinary Oncology, University of South Florida, Tampa, FL, USA. Blood, (November 16, 2001) Vol. 98, No. 11 Part 1, pp. 474a. print. Meeting Info.: 43rd Annual Meeting of the American Society of Hematology, Part 1. Orlando, Florida, USA. December 07-11, 2001. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971. Language: English.

AB Evasion of immune surveillance is a key step in malignant progression. Recent reports suggest that the tumor microenvironment may provide a heterologous network of survival signals that promote the progression and survival of hematopoietic malignancies. This network may involve soluble factors, and/or direct cellular contact with extracellular matrix (ECM) components and other cells. Therefore, interactions between transformed cells and their environment may initiate events that confer resistance to apoptosis and facilitate immune evasion. In this report, we demonstrate that beta1 integrin-mediated adhesion to fibronectin inhibits CD95-induced caspase-8 activation and apoptosis in hematologic cancer cell lines. Flow cytometric and Western blot analysis revealed no alterations in CD95 surface expression or total protein levels following adhesion to FN. Moreover, adhesion to FN did not alter agonist antibody binding to CD95. The reduced activation of procaspase-8, in the face of equal agonist antibody/receptor binding, indicated that the protective effect(s) of FN adhesion may occur at or upstream of procaspase-8, but downstream of CD95 cross-linking. These data suggested that FN adhesion may influence the death inducing signal complex (DISC) induced by CD95 aggregation. The recently cloned cellular homologue to viral-FLIP (FLICE-like inhibitory protein) c-FLIP/Casper/MRIT/**I-FLICE** /Usurpin/Flame/CLARP/CASH has been shown to inhibit CD95-mediated apoptosis and caspase-activation by acting as a physiological procaspase-8 dominant negative regulatory factor. Here, we show that this adhesion-dependent inhibition of CD95-mediated apoptosis correlated with enhanced c-FLIPL cytosolic solubility as compared to non-adhered cells. Cytosolic c-FLIPL protein preferentially associated with cytosolic FADD and localized to the Death Inducing Signal Complex (DISC) following CD95 ligation in adherent cells. The incorporation of c-FLIPL in the DISC prevented procaspase-8 processing and activation of the effector phase of apoptosis. Using subcellular fractionation we demonstrated that adhesion to fibronectin increased c-FLIPL cytosolic solubility and availability for FADD binding by redistributing c-FLIPL from a pre-existing membrane associated fraction to a cytosolic fraction. RNase protection assay and protein incorporation assays demonstrated that the increased cytosolic availability of c-FLIPL for FADD binding was not related to increased levels of RNA or protein synthesis, respectively. These data show that cell adhesion of anchorage independent cells to fibronectin provides a novel mechanism of resistance to cytotoxic elimination by regulating the cellular localization and availability of c-FLIPL and inhibiting CD95-mediated programmed cell death.

L4 ANSWER 20 OF 34 CAPLUS COPYRIGHT 2004 ACS on STN

2001:539423 Document No. 136:198848 Characterization of the human FLICE-inhibitory protein locus and comparison of the anti-apoptotic activity of four different FLIP isoforms. Djerbi, M.; Darreh-Shori, T.; Zhivotovsky, B.; Grandien, A. (Department of Immunology, the Wenner-Gren Institute, University of Stockholm, Stockholm, S-106 91, Swed.). Scandinavian Journal of Immunology, 54(1/2), 180-189 (English) 2001.
CODEN: SJIMAX. ISSN: 0300-9475. Publisher: Blackwell Science Ltd..

AB Death receptor-mediated apoptosis is involved in the regulation of immune responses and in the maintenance of immunol. tolerance. FLICE-inhibitory proteins (FLIPs) are important modulators of death receptor-mediated apoptosis. To date, the FLIP family encompasses multiple members, of which some are reported to be antiapoptotic and others pro-apoptotic. This led the authors to investigate the activity of several FLIP proteins in vitro. Concomitant with the cloning of various FLIP isoforms, a new and unexpected member of the FLIP family, denoted FLIPR, was isolated from the human Burkitt lymphoma B-cell line Raji. During the characterization of FLIPR, the genomic sequence of human FLIP was found in the NCBI

GenBank. This enabled the authors to present the complete exon-intron constellation of the human FLIP gene and the generation of all known human FLIP isoforms by alternative splicing. The authors show that the human FLIP gene with a size of approx. 48 kb, consists of at least 14 exons and can give rise to 11 distinct isoforms by alternative splicing. When studying the activity of some of these isoforms, including FLIPR, they all efficiently inhibited Fas-mediated apoptosis in A20 B lymphoma cells by impeding caspase-8, -3 and -7 activity as well as poly(ADP-ribose) polymerase (PARP) cleavage.

L4 ANSWER 21 OF 34 CAPLUS COPYRIGHT 2004 ACS on STN
2000:725658 Document No. 133:295359 Inhibition of T cell apoptosis by an anti-apoptotic fusion polypeptide comprising FLIP protein and TAT. Paya, Carlos; Algeciras-Schminich, Alicia (Mayo Foundation for Medical Education and Research, USA). PCT Int. Appl. WO 2000059935 A1 20001012, 89 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US9002 20000405. PRIORITY: US 1999-PV127867 19990405; US 1999-PV128021 19990406.

AB A chimeric moiety useful to inhibit apoptosis is provided. The chimeric moiety comprises at least a portion of an anti-apoptotic protein in combination with a transport moiety effective to transport the chimeric moiety across a cell membrane. The anti-apoptotic protein comprises cellular or viral FLIP, or a portion of the FLIP protein, and the transport moiety comprises a viral peptide or polypeptide such as the tat protein of lentiviruses. The invention is based on the discovery that TCR activation decreases the steady state protein levels of FLIP, an inhibitor of the Fas signaling pathway. Reconstitution of intracellular FLIP levels by the addition of a soluble TAT-FLIP chimera complete restored resistance to Fas-mediated apoptosis in TCR-stimulated primary T cells. Inhibition of interleukin-2 production by cyclosporin A, or inhibition of interleukin-2 signaling by rapamycin or anti-interleukin-2 neutralizing antibodies, prevented the decrease of FLIP levels and conferred resistance to Fas-mediated apoptosis following T cell activation. Using cell cycle blocking agents, activated T cells arrested in G1 phase were found to contain high levels of FLIP protein, whereas activated T cells arrested in S phase had decreased FLIP protein levels. In addition, the soluble TAT-FLIP chimera inhibited HIV-mediated T cell death.

L4 ANSWER 22 OF 34 CAPLUS COPYRIGHT 2004 ACS on STN
2000:857201 Document No. 134:130230 Clonality and longevity of CD4+CD28null T cells are associated with defects in apoptotic pathways. Vallejo, Abbe N.; Schirmer, Michael; Weyand, Cornelia M.; Goronzy, Jorg J. (Departments of Medicine and Immunology, Mayo Clinic and Foundation, Rochester, MN, 55905, USA). Journal of Immunology, 165(11), 6301-6307 (English) 2000. CODEN: JOIMA3. ISSN: 0022-1767. Publisher: American Association of Immunologists.

AB CD4+CD28null T cells are oligoclonal lymphocytes rarely found in healthy individuals younger than 40 yr, but are found in high frequencies in elderly individuals and in patients with chronic inflammatory diseases. Contrary to paradigm, they are functionally active and persist over many years. Such clonogenic potential and longevity suggest altered responses to apoptosis-inducing signals. In this study, the authors show that CD4+CD28null T cells are protected from undergoing activation-induced cell death. Whereas CD28+ T cells underwent Fas-mediated apoptosis upon crosslinking of CD3, CD28null T cells were highly resistant. CD28null T cells were found to progress through the cell cycle, and cells at all stages of the cell cycle were resistant to apoptosis, unlike their CD28+ counterparts. Neither the activation-induced up-regulation of the IL-2R α-chain (CD25) nor the addition of exogenous IL-2 renders them

susceptible to Fas-mediated apoptosis. These properties of CD28null T cells were related to high levels of Fas-associated death domain-like IL-1-converting enzyme-like inhibitory protein, an inhibitor of Fas signaling that is normally degraded in T cells following activation in the presence of IL-2. Consistent with previous data showing protection of CD28null cells from spontaneous cell death, the present studies unequivocally show dysregulation of apoptotic pathways in CD4+CD28null T cells that favor their clonal outgrowth and maintenance in vivo.

L4 ANSWER 23 OF 34 CAPLUS COPYRIGHT 2004 ACS on STN
2000:857200 Document No. 134:130229 TCR-mediated up-regulation of c-FLIPshort correlates with resistance toward CD95-mediated apoptosis by blocking death-inducing signaling complex activity. Kirchhoff, Sabine; Muller, Wolfgang W.; Krueger, Andreas; Schmitz, Ingo; Krammer, Peter H. (Tumor Immunology Program, German Cancer Research Center, Heidelberg, D-69120, Germany). Journal of Immunology, 165(11), 6293-6300 (English) 2000. CODEN: JOIMA3. ISSN: 0022-1767. Publisher: American Association of Immunologists.

AB To investigate apoptosis resistance upon restimulation in human peripheral blood T lymphocytes, the authors used the following in vitro model. This model represents the main features of T cell reactivity: freshly isolated PHA-activated T cells cultured in IL-2 for a prolonged period of time develop a CD95 (APO-1/Fas) apoptosis-sensitive phenotype. These T cells represent activation-induced cell death-sensitive T cells during the down phase of an immune response. A fraction of apoptosis-sensitive activated T cells becomes apoptosis resistant upon TCR/CD3 restimulation. CD95 apoptosis sensitivity requires formation of a functional receptor associated death-inducing signaling complex (DISC), i.e., a protein complex of CD95 receptors, the adaptor Fas-associated death domain protein (FADD)/MORT1 and caspase-8 (FADD-like IL-1β-converting enzyme (FLICE), MACH, Mch5). The authors identified activation of procaspase-8 at the DISC as the main target for the protective activity of TCR/CD3 restimulation. The authors found that procaspase-8 cleavage is reduced in T cells after TCR/CD3 restimulation. In addition, the authors detected up-regulation of c-FLIPS (the short splice variant of the cellular FLICE inhibitory protein) and strongly enhanced recruitment of c-FLIPS into the DISC. These data suggest that the recruitment of c-FLIPS into the DISC results in reduced DISC and caspase-8 activity.

L4 ANSWER 24 OF 34 CAPLUS COPYRIGHT 2004 ACS on STN
2000:735478 Document No. 134:4016 Activation of the NF-κB pathway by caspase 8 and its homologs. Chaudhary, Preet M.; Eby, Michael T.; Jasmin, Alan; Kumar, Arvind; Liu, Li; Hood, Leroy (Hamon Center for Therapeutic Oncology Research, UT Southwestern Medical Center, Dallas, TX, 75390-8593, USA). Oncogene, 19(39), 4451-4460 (English) 2000. CODEN: ONCNES. ISSN: 0950-9232. Publisher: Nature Publishing Group.

AB Caspase 8 is the most proximal caspase in the caspase cascade and has been known for its role in the mediation of cell death by various death receptors belonging to the TNFR family. The authors have discovered that caspase 8 can activate the NF-κB pathway independent of its activity as a pro-apoptotic protease. This property is localized to its N-terminal prodomain, which contains two homologous death effector domains (DEDs). Caspase 10 and MRIT, two DEDs-containing homologs of Caspase 8, can similarly activate the NF-κB pathway. Dominant-neg. mutants of the caspase 8 prodomain can block NF-κB induced by caspase 8, FADD, and several death receptors belonging to the TNFR family. Caspase 8 can interact with multiple proteins known to be involved in the activation of the NF-κB pathway, including the serine-threonine kinases RIP, NIK, IKK1, and IKK2. Thus, DEDs-containing caspases and caspase homolog(s) may have functions beyond their known role in the mediation of cell death.

L4 ANSWER 25 OF 34 CAPLUS COPYRIGHT 2004 ACS on STN
2000:76863 Document No. 133:3208 Expression of cellular FLICE-inhibitory protein in human coronary arteries and in a rat vascular injury model. Imanishi, Toshio; McBride, Jonathan; Ho, Quoc; O'Brien, Kevin D.;

Schwartz, Stephen M.; Han, David K. M. (Department of Pathology, University of Washington, Seattle, WA, 98195, USA). American Journal of Pathology, 156(1), 125-137 (English) 2000. CODEN: AJPAA4. ISSN: 0002-9440. Publisher: American Society for Investigative Pathology.

AB The authors previously isolated MACH-related inducer of toxicity (MRIT), a homolog of caspase 8. MRIT, also known as c-FLICE-inhibitory protein (c-FLIP), is an enzymically inactive homolog of caspase 8 with homol. to viral FLIP (v-FLIP). Because of this homol. and resemblance to dominant neg. proteins, c-FLIP is widely believed to be an antagonist to the death receptor-initiated apoptotic pathways that use caspase 8. The authors generated a polyclonal antibody, MAG1, and show that this antibody specifically recognizes two splice forms, long form (c-FLIPl) and short form (c-FLIPs). By in situ hybridization and immunohistochem., the authors demonstrate that c-FLIP is expressed in endothelial cells, macrophages, and smooth muscle cells (SMCs) both in human coronary arteries and in cultured cells. In uninjured rat carotid arteries, c-FLIP protein is abundant in the vascular media. After balloon angioplasty, c-FLIP protein is rapidly down-regulated in medial SMCs for 2 wk and regains expression by 4 wk. In contrast, the neointima is strongly immunoreactive to c-FLIP from day 7 after the initial injury and remains strongly immunoreactive until 4 to 6 wk. Similarly there is strong c-FLIP immunoreactivity in SMCs from nonatherosclerotic diffuse intimal thickening and in the overlying endothelial cells. In contrast, c-FLIP immunoreactivity is uneven and often absent in SMCs within the atherosclerotic plaque. Double labeling with c-FLIP antibody and terminal deoxynucleotidyl-transferase-mediated UDP end labeling (TUNEL) in the injured rat common carotid artery show that TUNEL-pos. cells in the first 2 days after injury lack detectable c-FLIP, suggested a role for caspase 8 in this form of death. In contrast, there is no correlation of c-FLIP with the spontaneous elevation in death of intima seen at 7 days after injury. For human atherosclerotic plaques, the majority of TUNEL-pos. cells lack detectable c-FLIP. The expression pattern of c-FLIP and the relation between c-FLIP and TUNEL suggest a role for c-FLIP- and caspase 8-driven death in control of viability of the cells of the atherosclerotic intima.

L4 ANSWER 26 OF 34 CAPLUS COPYRIGHT 2004 ACS on STN

1999:549366 Document No. 131:153759 Cellular FLIP compositions for treatment of arteriosclerotic disorders. Walsh, Kenneth (St. Elizabeth's Medical Center of Boston, Inc., USA). PCT Int. Appl. WO 9942570 A1 19990826, 105 pp. DESIGNATED STATES: W: AU, CA, JP, US; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US3558 19990219. PRIORITY: US 1998-PV75471 19980220.

AB A method for treating conditions associated with vascular wall inflammation, particularly arteriosclerosis and vascular injury is provided. The method involves administering to subjects in need of such treatment an effective amount of a FLIP (FLICE inhibitory protein) mol. The method is based on the discovery that functional Fas ligand is expressed on the normal vascular endothelium and that expression of the Fas ligand is down-regulated by the inflammatory cytokine, tumor necrosis factor-α (TNFα). Further, (1) adenovirus-mediated constitutive Fas ligand expression by the endothelium reduces the leukocyte extravasation by local treatment with TNFα, (2) functional Fas ligand-expressing endothelial cells are not sensitive to Fas ligand-induced apoptosis, (3) dysfunctional Fas ligand-expressing endothelial cells (e.g., cells exposed to oxidized lipid) are sensitive to Fas ligand-induced apoptosis, and (4) dysfunctional endothelial cells exhibit a higher death rate and reduced cellular FLIP mRNA levels compared to endothelial cells that are not so exposed. Thus, there is a requirement for the Fas/Fas ligand pathway in vascular endothelial cell apoptosis induced by oxidized LDL that down-regulates FLIP mRNA transcription. Procedures for preparing a replication-defective recombinant adenoviral vector containing the cDNA encoding FLIP and delivering the vector by percutaneous arterial gene transfer are presented.

L4 ANSWER 27 OF 34 MEDLINE on STN DUPLICATE 2
2000042314. PubMed ID: 10573518. Cholangiocarcinomas express Fas ligand and disable the Fas receptor. Que F G; Phan V A; Phan V H; Celli A; Batts K; LaRusso N F; Gores G J. (Division of Gastroenterologic and General Surgery, Mayo Medical School, Clinic, and Foundation, Rochester, MN 55905, USA.. que.florencia@mayo.edu) . Hepatology (Baltimore, Md.), (1999 Dec) 30 (6) 1398-404. Journal code: 8302946. ISSN: 0270-9139. Pub. country: United States. Language: English.

AB Cholangiocarcinoma is a highly-malignant adenocarcinoma originating from cholangiocytes. Current concepts support escape from immune surveillance using aberrant expression of Fas ligand (FasL) and dysregulation of receptor (FasR) signaling as a potential mechanism for tumor progression. Our aims were to determine if altered expression of FasR and FasL or changes in expression of FLICE inhibitor (**I-FLICE**) allow cholangiocarcinoma cells to escape immune surveillance. Human cholangiocarcinoma cell lines were evaluated for the functional expression of FasR and FasL by (1) quantitating apoptosis after incubation of cells with agonistic antibodies and (2) an in vitro cell death assay involving coculture of cholangiocarcinoma cells with Fas-sensitive thymocytes. **I-FLICE** antisense treatment was performed by stable transfection with complementary DNA (cDNA) for **I-FLICE** in the reverse orientation. We found that normal cholangiocytes in vivo express FasL. Human cholangiocarcinoma cell lines express both FasL and FasR and **I-FLICE.** FasL expressed by cholangiocarcinomas in vitro induced lymphocyte cell death (70% after 24 hours). Despite the expression of FasR, exposure of the cells to agonistic antibodies (500 ng/mL) induced only minimal apoptosis in the Jurkat cells. Antisense treatment of cholangiocarcinomas in vitro with **I-FLICE** reduced protein expression of **I-FLICE** by 90% to 95% and increased Fas-mediated apoptosis 2-fold. We concluded that cholangiocarcinomas escape immune surveillance either by disabling FasR signaling through the expression of **I-FLICE** and/or increased FasL expression to induce apoptosis of invading T cells. Reduction of **I-FLICE** expression in cholangiocarcinoma cells restored Fas-mediated apoptosis. Therapeutic maneuvers to inhibit expression of **I-FLICE** may aid in the treatment of cholangiocarcinoma.

L4 ANSWER 28 OF 34 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN
1999:877688 The Genuine Article (R) Number: 239XE. Knockout of **I-FLICE** restores sensitivity to Fas and TRAIL in a cholangiocarcinoma cell line. Que F G (Reprint); Phan V A; Phan V H; Larusso N F; Gores G J. MAYO CLIN, ROCHESTER, MN. HEPATOLOGY (OCT 1999) Vol. 30, No. 4, Part 2, Supp. [S], pp. 896-896. Publisher: W B SAUNDERS CO . INDEPENDENCE SQUARE WEST CURTIS CENTER, STE 300, PHILADELPHIA, PA 19106-3399. ISSN: 0270-9139. Pub. country: USA. Language: English.

L4 ANSWER 29 OF 34 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
1999:496514 Document No.: PREV199900496514. Knockout of **I-FLICE** restores sensitivity to Fas and trail in a cholangiocarcinoma cell line. Que, Florencia G. [Reprint author]; Phan, Vy. A. [Reprint author]; Phan, Van H. [Reprint author]; Larusso, Nicholas F. [Reprint author]; Gores, Gregory J. [Reprint author]. Mayo Clin, Rochester, MN, USA. Hepatology, (Oct., 1999) Vol. 30, No. 4 PART 2, pp. 384A. print.
Meeting Info.: 50th Annual Meeting and Postgraduate Courses of the American Association for the Study of Liver Diseases. Dallas, Texas, USA. November 5-9, 1999. American Association for the Study of Liver Diseases.
CODEN: HPTLD9. ISSN: 0270-9139. Language: English.

L4 ANSWER 30 OF 34 MEDLINE on STN DUPLICATE 3
1999452132. PubMed ID: 10524501. The role of Fas-mediated apoptosis in

thyroid autoimmune disease. Borgerson K L; Bretz J D; Baker J R Jr. (Department of Internal Medicine, University of Michigan, Ann Arbor, USA.) Autoimmunity, (1999) 30 (4) 251-64. Ref: 70. Journal code: 8900070. ISSN: 0891-6934. Pub. country: Switzerland. Language: English.

AB Apoptosis is a carefully regulated mechanism of cell death that differs from necrosis and plays an important role in normal tissue development and homeostasis, as well as disease processes. Apoptosis also plays an important role in autoimmunity. Defective apoptosis can cause systemic autoimmunity by allowing the survival of autoreactive lymphocytes. It may also be involved in the pathogenesis of organ-specific autoimmune diseases, such as Hashimoto's thyroiditis, through altered target organ susceptibility. Apoptosis signaling pathways can be initiated through activation of death receptors. One of these pathways employs the death receptor Fas and its ligand (FasL). Fas expression and death pathway signaling have been demonstrated in the thyroid, but there is controversy surrounding the expression of FasL and its role in thyroid autoimmunity. A number of proteins, including FAP-1, Bcl-2 and **I-FLICE** may regulate the Fas pathway in the thyroid and provide potential mechanisms for modifying the pathogenesis of autoimmune thyroid disease.

L4 ANSWER 31 OF 34 CAPLUS COPYRIGHT 2004 ACS on STN

1998:509282 Document No. 129:132226 Cloning and cDNA sequence of human **I-FLICE** inhibitor of tumor necrosis factor receptor-1 and CD-95 induced apoptosis. Ni, Jian; Rosen, Craig A.; Dixit, Vishva M.; Gentz, Reiner L.; Kenny, Joseph J. (Human Genome Sciences, Inc., USA; The Regents of the University of Michigan). PCT Int. Appl. WO 9831801 A1 19980723, 119 pp. DESIGNATED STATES: W: CA, JP; RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1998-US969 19980121. PRIORITY: US 1997-34205 19970121; US 1997-54800 19970805.

AB The present invention relates to a novel **I-FLICE**-1 or **I-FLICE**-2 protein which is a novel inhibitor of tumor necrosis factor receptor-1 and CD-95 induced apoptosis. In particular, cDNA mols. encoding the human **I-FLICE**-1 or **I-FLICE**-2 protein were isolated from human umbilical vein endothelial cell cDNA libraries. **I-FLICE**-1 cDNA contains an open reading frame for a 480-amino acid residue protein, and **I-FLICE**-2 cDNA encodes a 358-amino acid protein. **I-FLICE**-1 was also identified in cDNA libraries from smooth muscle, and **I-FLICE**-2 cDNA was identified in the cerebellum. **I-FLICE**-1 binds to FLICE proteinase and Mch4/FLICE2, and its overexpression results in inhibition of cell death induced by tumor necrosis factor receptor-1 or CD-95. **I-FLICE**-1 or **I-FLICE**-2 polypeptides are also provided as are vectors, host cells and recombinant methods for producing the same. The invention further relates to screening methods for identifying agonists and antagonists of **I-FLICE**-1 or **I-FLICE**-2 activity. Also provided are therapeutic methods for treating diseases and disorders associated with apoptosis.

L4 ANSWER 32 OF 34 MEDLINE on STN DUPLICATE 4

1998451441. PubMed ID: 9780161. FLIP prevents apoptosis induced by death receptors but not by perforin/granzyme B, chemotherapeutic drugs, and gamma irradiation. Kataoka T; Schroter M; Hahne M; Schneider P; Irmler M; Thome M; Froelich C J; Tschopp J. (Institute of Biochemistry, University of Lausanne, Epalinges, Switzerland.) Journal of immunology (Baltimore, Md. : 1950), (1998 Oct 15) 161 (8) 3936-42. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB FLICE-inhibitory protein, FLIP (Casper/**I-FLICE**/FLAME-1/CASH/CLARP/MRIT), which contains two death effector domains and an inactive caspase domain, binds to FADD and caspase-8, and thereby inhibits death receptor-mediated apoptosis. Here, we characterize the inhibitory effect of FLIP on a variety of apoptotic pathways. Human Jurkat T cells undergoing Fas ligand-mediated apoptosis in response to CD3 activation were completely resistant when transfected with FLIP. In

contrast, the presence of FLIP did not affect apoptosis induced by granzyme B in combination with adenovirus or perforin. Moreover, the Fas ligand, but not the perforin/granzyme B-dependent lytic pathway of CTL, was inhibited by FLIP. Apoptosis mediated by chemotherapeutic drugs (i.e., doxorubicin, etoposide, and vincristine) and gamma irradiation was not affected by FLIP or the absence of Fas, indicating that these treatments can induce cell death in a Fas-independent and FLIP-insensitive manner.

L4 ANSWER 33 OF 34 MEDLINE on STN DUPLICATE 5

1999218584. PubMed ID: 10200473. Cell death attenuation by 'Usurpin', a mammalian DED-caspase homologue that precludes caspase-8 recruitment and activation by the CD-95 (Fas, APO-1) receptor complex. Rasper D M; Vaillancourt J P; Hadano S; Houtzager V M; Seiden I; Keen S L; Tawa P; Xanthoudakis S; Nasir J; Martindale D; Koop B F; Peterson E P; Thornberry N A; Huang J; MacPherson D P; Black S C; Hornung F; Lenardo M J; Hayden M R; Roy S; Nicholson D W. (Department of Biochemistry and Molecular Biology, Merck Frosst Centre for Therapeutic Research, Pointe Claire-Dorval, Quebec, Canada, H9R 4P8.) Cell death and differentiation, (1998 Apr) 5 (4) 271-88. Journal code: 9437445. ISSN: 1350-9047. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Apoptotic cell suicide initiated by ligation of CD95 (Fas/APO-1) occurs through recruitment, oligomerization and autocatalytic activation of the cysteine protease, caspase-8 (MACH, FLICE, Mch5). An endogenous mammalian regulator of this process, named Usurpin, has been identified (aliases for Usurpin include CASH, Casper, CLARP, FLAME-1, FLIP, **I-FLICE** and MRIT). This protein is ubiquitously expressed and exists as at least three isoforms arising by alternative mRNA splicing. The Usurpin gene is comprised of 13 exons and is clustered within approximately 200 Kb with the caspase-8 and -10 genes on human chromosome 2q33-34. The Usurpin polypeptide has features in common with pro-caspase-8 and -10, including tandem 'death effector domains' on the N-terminus of a large subunit/small subunit caspase-like domain, but it lacks key residues that are necessary for caspase proteolytic activity, including the His and Cys which form the catalytic substrates diad, and residues that stabilize the P1 aspartic acid in substrates. Retro-mutation of these residues to functional caspase counterparts failed to restore proteolytic activity, indicating that other determinants also ensure the absence of catalytic potential. Usurpin heterodimerized with pro-caspase-8 in vitro and precluded pro-caspase-8 recruitment by the FADD/MORT1 adapter protein. Cell death induced by CD95 (Fas/APO-1) ligation was attenuated in cells transfected with Usurpin. In vivo, a Usurpin deficit was found in cardiac infarcts where TUNEL-positive myocytes and active caspase-3 expression were prominent following ischemia/reperfusion injury. In contrast, abundant Usurpin expression (and a caspase-3 deficit) occurred in surrounding unaffected cardiac tissue, suggesting reciprocal regulation of these pro- and anti-apoptotic molecules in vivo. Usurpin thus appears to be an endogenous modulator of apoptosis sensitivity in mammalian cells, including the susceptibility of cardiac myocytes to apoptotic death following ischemia/ reperfusion injury.

L4 ANSWER 34 OF 34 MEDLINE on STN DUPLICATE 6

97362203. PubMed ID: 9211860. **I-FLICE**, a novel inhibitor of tumor necrosis factor receptor-1- and CD-95-induced apoptosis. Hu S; Vincenz C; Ni J; Gentz R; Dixit V M. (Department of Pathology, University of Michigan Medical School, Ann Arbor, Michigan 48109, USA.) Journal of biological chemistry, (1997 Jul 11) 272 (28) 17255-7. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB The pivotal discovery that the death proteases caspase 8 (FLICE) and caspase 10 (Mch4/FLICE2) are recruited to the CD-95 and tumor necrosis factor receptor-1 signaling complexes suggested a mechanism used by these cytotoxic receptors to initiate apoptosis. In this report, we describe the cloning and characterization of **I-FLICE**, a novel

inhibitor of tumor necrosis factor receptor-1- and CD-95-induced apoptosis. The overall architecture of **I-FLICE** is strikingly similar to that of FLICE and Mch4/FLICE2. However, **I-FLICE** lacks both a catalytic active site and residues that form the substrate binding pocket, in keeping with its dominant negative inhibitory function. **I-FLICE** is the first example of a catalytically inert caspase that can inhibit apoptosis.

=> s caspase 10 inhibitor
L5 15 CASPASE 10 INHIBITOR

=> dup remove l5
PROCESSING COMPLETED FOR L5
L6 6 DUP REMOVE L5 (9 DUPLICATES REMOVED)

=> d l6 1-6 cbib abs

L6 ANSWER 1 OF 6 MEDLINE on STN DUPLICATE 1
2004397664. PubMed ID: 15301743. Diosgenin induces apoptosis in HeLa cells via activation of caspase pathway. Hou Rui; Zhou Qiu-Li; Wang Ben-Xiang; Tashiro Shin-Ichi; Onodera Satoshi; Ikejima Takashi. (China-Japan Research Institute of Medical and Pharmaceutical Sciences, Shenyang Pharmaceutical University, Shenyang 110016, China.) Acta pharmacologica Sinica, (2004 Aug) 25 (8) 1077-82. Journal code: 100956087. ISSN: 1671-4083. Pub. country: China. Language: English.

AB AIM: To investigate the mechanism of diosgenin-induced HeLa cell apoptosis. METHODS: HeLa cell growth was measured by MTT method. Apoptosis was detected by electron microscopy and agarose gel electrophoresis. Ratio of apoptotic cells was measured by APO-BRDU kit. Cell cycle distribution and changes of mitochondrial membrane potential were monitored by flow cytometry. Caspase activities were assayed by caspase apoptosis detection kit. Western blot analysis was used to evaluate the level of mitochondrial Bcl-2 expression. RESULTS: Diosgenin inhibited HeLa cell growth. HeLa cells treated with diosgenin showed typical characteristics of apoptosis including the morphological changes and DNA fragmentation. Caspase family inhibitor (z-VAD-fmk), caspase-9 inhibitor (Ac-AAVALPAVLLALLAPLEHD-CHO), and caspase-3 inhibitor (z-DEVD-fmk) partially prevented diosgenin-induced apoptosis, but not caspase-8 inhibitor (z-IETD-fmk) and **caspase-10 inhibitor** (z-AEVD-fmk). Diosgenin caused reduction of mitochondrial membrane potential and down-regulated Bcl-2 expression. CONCLUSION: Diosgenin induced HeLa cell apoptosis through caspase pathway.

L6 ANSWER 2 OF 6 MEDLINE on STN DUPLICATE 2
2004313789. PubMed ID: 15215653. Dracorhodin perchlorate induces apoptosis via activation of caspases and generation of reactive oxygen species. Xia Mingyu; Wang Dong; Wang Minwei; Tashiro Shin-Ichi; Onodera Satoshi; Minami Mutsuhiko; Ikejima Takashi. (China-Japan Research Institute of Medical and Pharmaceutical Sciences, Shenyang Pharmaceutical University, Shenyang, China.) Journal of pharmacological sciences, (2004 Jun) 95 (2) 273-83. Journal code: 101167001. ISSN: 1347-8613. Pub. country: Japan. Language: English.

AB Dracorhodin perchlorate inhibited proliferation of several tumor cell lines. The drug induced oligonucleosomal fragmentation of DNA in HeLa cells and increased caspase-3, -8, -9 activities followed by the degradation of caspase-3 substrates, inhibitor of caspase-dependent DNase, and poly-(ADP-ribose) polymerase. It also increased caspase-1 activity and a caspase-1 inhibitor, Ac-YVAD-cmk, and a **caspase-10 inhibitor** z-AEVD-fmk, also reduced dracorhodin-perchlorate-induced HeLa cell death. Dracorhodin perchlorate decreased the expression of anti-apoptotic mitochondrial protein, Bcl-X(L), but not Bcl-2; and it increased the expression of pro-apoptotic protein, Bax. Dracorhodin perchlorate induced a sustained generation of reactive oxygen species (ROS) in HeLa cells; caspase-1 inhibitor, Ac-YVAD-cmk, and caspase-3

inhibitor, z-DEVD-fmk, attenuated the generation of ROS. Taken together, our results indicate that dracorhodin perchlorate alters the intracellular redox status, changed the balance of Bcl-X(L) and Bax protein expression, and induces apoptosis through caspase pathways in HeLa cells.

L6 ANSWER 3 OF 6 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

2004022400 EMBASE The effect of specific caspase inhibitors on TNF-α and butyrate-induced apoptosis of intestinal epithelial cells. Jones S.A.; Butler R.N.; Sanderson I.R.; Wilson J.W.. J.W. Wilson, Inst. of Cell and Molecular Sciences, Qu. Mary Sch. of Med. and Dentistry, University of London, London EC1A 7BE, United Kingdom. j.w.wilson@qmul.ac.uk. Experimental Cell Research 292/1 (29-39) 1 Jan 2004. Refs: 33. ISSN: 0014-4827. CODEN: ECREAL. Pub. Country: United States. Language: English. Summary Language: English.

AB Tumour necrosis factor-α (TNF-α)-induced intestinal epithelial cell apoptosis may contribute to mucosal injury in inflammatory bowel disease. Inhibition of TNF-α-induced apoptosis, using specific caspase inhibitors could, therefore, be of benefit in the treatment of disease. In vitro, CaCo-2 colonic epithelial cells are refractory to apoptosis induced by TNF-α alone; however, TNF-α can act synergistically with the short-chain fatty acid (SCFA) and colonic fermentation product, butyrate, to promote apoptosis. TNF-α/butyrate-induced apoptosis was characterised by nuclear condensation and fragmentation and caspase-3 activation. Inhibitors of caspase-8 (z-IETD.fmk) and caspase-10 (z-AEVD.fmk) significantly reduced TNF-α/butyrate-induced apoptosis, based on nuclear morphology and terminal deoxynucleotide transferase-mediated dUTP-biotin nick-end labelling (TUNEL), although caspase inhibition was associated with a significant increase in cells demonstrating atypical nuclear condensation. Inclusion of atypical cells in calculations of total cell death, still demonstrated that z-IETD.fmk and z-AEVD.fmk (in combination) significantly reduced cell death. Reduction in cell death was associated with maintenance of viable cell number. Transmembrane resistance was also used a measure of the ability of caspase inhibitors to prevent TNF-α/butyrate-mediated damage to epithelial monolayers. TNF-α/butyrate resulted in a significant fall in transmembrane resistance, which was prevented by pre-treatment with z-IETD.fmk, but not z-AEVD.fmk. In conclusion, synthetic caspase inhibitors can reduce the apoptotic response of CaCo-2 colonic epithelial cells to TNF-α/butyrate, improve the maintenance of viable cell numbers and block loss of transmembrane resistance. We hypothesise that caspase inhibition could be a useful therapeutic goal in the treatment of inflammatory bowel conditions, such as ulcerative colitis. .COPYRGT. 2003 Elsevier Inc. All rights reserved.

L6 ANSWER 4 OF 6 MEDLINE on STN DUPLICATE 3

2003132410. PubMed ID: 12646627. Galectin-9 induces apoptosis through the calcium-calpain-caspase-1 pathway. Kashio Yumiko; Nakamura Kazuhiro; Abedin Mohammad J; Seki Masako; Nishi Nozomu; Yoshida Naoko; Nakamura Takanori; Hirashima Mitsuomi. (Department of Immunology and Immunopathology, Kagawa Medical University, Ikenobe, Miki-cho, Kita-gun, Kagawa, Japan.) Journal of immunology (Baltimore, Md. : 1950), (2003 Apr 1) 170 (7) 3631-6. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB Galectin-9 (Gal-9) induced the apoptosis of not only T cell lines but also of other types of cell lines in a dose- and time-dependent manner. The apoptosis was suppressed by lactose, but not by sucrose, indicating that beta-galactoside binding is essential for Gal-9-induced apoptosis. Moreover, Gal-9 required at least 60 min of Gal-9 binding and possibly de novo protein synthesis to mediate the apoptosis. We also assessed the apoptosis of peripheral blood T cells by Gal-9. Apoptosis was induced in both activated CD4(+) and CD8(+) T cells, but the former were more susceptible than the latter. A pan-caspase inhibitor (Z-VAD-FMK)

inhibited Gal-9-induced apoptosis. Furthermore, a caspase-1 inhibitor (Z-YVAD-FMK), but not others such as Z-IETD-FMK (caspase-8 inhibitor), Z-LEHD-FMK (caspase-9 inhibitor), and Z-AEVD-FMK (**caspase-10 inhibitor**), inhibited Gal-9-induced apoptosis. We also found that a calpain inhibitor (Z-LLY-FMK) suppresses Gal-9-induced apoptosis, that Gal-9 induces calcium (Ca(2+)) influx, and that either the intracellular Ca(2+) chelator BAPTA-AM or an inositol trisphosphate inhibitor 2-aminoethoxydiphenyl borate inhibits Gal-9-induced apoptosis. These results suggest that Gal-9 induces apoptosis via the Ca(2+)-calpain-caspase-1 pathway, and that Gal-9 plays a role in immunomodulation of T cell-mediated immune responses.

L6 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2004 ACS on STN
2002:696003 Document No. 137:215798 Anti-apoptotic agents or interleukin 1β converting enzyme (ICE/CED-3) inhibitors for preserving antigenicity of markers associated with diseases. Aja, Teresa; Ching, Brett W.; Gladstone, Patricia L. (Idun Pharmaceuticals, Inc., USA). PCT Int. Appl. WO 2002070544 A2 20020912, 148 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US7208 20020301. PRIORITY: US 2001-PV272750 20010302.

AB The present invention relates generally to programmed cell death and specifically to methods, compns., and kits for preserving or enhancing antigenicity of markers associated with disease by utilizing inhibitors of apoptosis including interleukin-1β-converting enzyme (ICE)/CED-3 family inhibitors.

L6 ANSWER 6 OF 6 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
2000:295747 Document No.: PREV200000295747. Fas-activation inhibits activation of heat shock factor (hsF)-1 and expression of heat shock protein (hsp) 70. Schett, G. [Reprint author]; Steiner, C.-W.; Winkler, S.; Graninger, W.; Smolen, J.; Xu, Q.; Steiner, G.. Abteilung fur Rheumatologie, Universitatsklinik fur Innere Medizin III, Wahringer Gurtel 18-20, A-1090, Wien, Austria. Acta Medica Austriaca, (2000) Vol. 27, No. 3, pp. 94-98. print.
CODEN: AMAUBB. ISSN: 0303-8173. Language: German.

AB Activation of heat shock factor (HSF)-1 DNA binding and heat shock protein (hsp)-70 expression enable resistance of cells to various forms of stress and maintain cell survival. Fas, a membrane-bound protein, is a central proapoptotic factor. Its activation leads to a cascade of events resulting in programmed cell death. Herein, these two mechanisms with contrary functions, promoting either cell survival or death, were addressed for their potential to inhibit each other's activation. Induction of Fas-mediated signalling was followed by a rapid decrease of HSF1 DNA binding and inducible hsp70 expression. Inhibition of HSF1 DNA binding was demonstrated to be based on absent hyperphosphorylation of HSF1 during FAS-signalling. These effects of Fas-activation on the HSF1/hsp70 stress response were blocked by ICE (**caspase 10**)-**inhibitors**, suggesting an ICE-mediated process. Furthermore, inhibition of HSF1/hsp70 was accompanied by an increase of apoptosis rates from 20 % to 50 % in response to heat stress. When analyzing Fas-mediated apoptosis in the presence of HSF1/hsp70 activation, decreased apoptosis rates were detected with induced expression of hsp70 but not with activation of HSF1-DNA binding alone. Thus, we conclude that inhibition of the HSF1/hsp70 stress response during Fas-mediated apoptosis and vice versa may facilitate a cell to pass a previously choosen pathway, stress resistance or apoptosis.

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or kenny j?/au)
L7        12395 (NI J?/AU OR ROSEN C?/AU OR DIXIT V?/AU OR GENTZ R?/AU OR HORIZO
                NTE-MG B?/AU OR KENNY J?/AU)

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L8            8 L7 AND I-FLICE

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'REOVE' IS NOT VALID.  VALID FILE NAMES ARE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH,
CAPLUS'
You have entered a file name of duplicates to keep that is not
referenced by any of the L#s specified for this DUPLICATE command.
The file names of duplicates that can be kept are listed above.
Please enter one of these file names.

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PROCESSING COMPLETED FOR L8
L9            4 DUP REMOVE L8 (4 DUPLICATES REMOVED)

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L9   ANSWER 1 OF 4  BIOSIS  COPYRIGHT (c) 2004 The Thomson Corporation.  on STN
2004:111285  Document No.: PREV200400114842. I-FLICE, a
     novel inhibitor of tumor necrosis factor receptor-1 and CD-95 induced
     apoptosis. Ni, Jian [Inventor, Reprint Author]; Rosen,
     Craig A. [Inventor]; Dixit, Vishva M. [Inventor];
     Gentz, Reiner L. [Inventor]; Kenny, Joseph J.
     [Inventor]. ASSIGNEE: Human Genome Sciences, Inc.; The Regents of the
     University of Michigan. Patent Info.: US 6680171 January 20, 2004.
     Official Gazette of the United States Patent and Trademark Office Patents,
     (Jan 20 2004) Vol. 1278, No. 3. http://www.uspto.gov/web/menu/patdata.html
     . e-file.
     ISSN: 0098-1133 (ISSN print). Language: English.
AB   The present invention relates to a novel I-FLICE-1 or
     I-FLICE-2 protein which is a novel inhibitor of INFR-1
     and CD-95 induced apoptosis.  In particular, isolated nucleic acid
     molecules are provided encoding the human I-FLICE-1 or
     I-FLICE-2 protein.  I-FLICE-1 or
     I-FLICE-2 polypeptides are also provided as are vectors,
     host cells and recombinant methods for producing the same.  The invention
     further relates to screening methods for identifying agonists and
     antagonists of I-FLICE-1 or I-FLICE
     -2 activity.  Also provided are therapeutic methods for treating diseases
     and disorders associated with apoptosis.

L9   ANSWER 2 OF 4  BIOSIS  COPYRIGHT (c) 2004 The Thomson Corporation.  on STN
2003:485623  Document No.: PREV200300485623. I-flice, a
     novel inhibitor of tumor necrosis factor receptor-1 and CD-95 induced
     apoptosis. Ni, Jian [Inventor, Reprint Author]; Rosen,
     Craig A. [Inventor]; Dixit, Vishva M. [Inventor];
     Gentz, Reiner L. [Inventor]; Kenny, Joseph J.
     [Inventor]. ASSIGNEE: Human Genome Sciences, Inc.; The Regents of the
     University of Michigan. Patent Info.: US 6623938 September 23, 2003.
     Official Gazette of the United States Patent and Trademark Office Patents,
     (Sep 23 2003) Vol. 1274, No. 4. http://www.uspto.gov/web/menu/patdata.html
     . e-file.
     ISSN: 0098-1133 (ISSN print). Language: English.
AB   The present invention relates to a novel I-FLICE-1 or
     I-FLICE-2 protein which is a novel inhibitor of TNFR-1
     and CD-95 induced apoptosis.  In particular, isolated nucleic acid
     molecules are provided encoding the human I-FLICE-1 or
     I-FLICE-2 protein.  I-FLICE-1 or
     I-FLICE-2 polypeptides are also provided as are vectors,
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host cells and recombinant methods for producing the same. The invention further relates to screening methods for identifying agonists and antagonists of **I-FLICE**-1 or **I-FLICE**-2 activity. Also provided are therapeutic methods for treating diseases and disorders associated with apoptosis.

L9 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2004 ACS on STN
1998:509282 Document No. 129:132226 Cloning and cDNA sequence of human **I-FLICE** inhibitor of tumor necrosis factor receptor-1 and CD-95 induced apoptosis. **Ni, Jian; Rosen, Craig A.; Dixit, Vishva M.; Gentz, Reiner L.; Kenny, Joseph J.** (Human Genome Sciences, Inc., USA; The Regents of the University of Michigan). PCT Int. Appl. WO 9831801 A1 19980723, 119 pp. DESIGNATED STATES: W: CA, JP; RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1998-US969 19980121. PRIORITY: US 1997-34205 19970121; US 1997-54800 19970805.

AB The present invention relates to a novel **I-FLICE**-1 or **I-FLICE**-2 protein which is a novel inhibitor of tumor necrosis factor receptor-1 and CD-95 induced apoptosis. In particular, cDNA mols. encoding the human **I-FLICE**-1 or **I-FLICE**-2 protein were isolated from human umbilical vein endothelial cell cDNA libraries. **I-FLICE**-1 cDNA contains an open reading frame for a 480-amino acid residue protein, and **I-FLICE**-2 cDNA encodes a 358-amino acid protein. **I-FLICE**-1 was also identified in cDNA libraries from smooth muscle, and **I-FLICE**-2 cDNA was identified in the cerebellum. **I-FLICE**-1 binds to FLICE proteinase and Mch4/FLICE2, and its overexpression results in inhibition of cell death induced by tumor necrosis factor receptor-1 or CD-95. **I-FLICE**-1 or **I-FLICE**-2 polypeptides are also provided as are vectors, host cells and recombinant methods for producing the same. The invention further relates to screening methods for identifying agonists and antagonists of **I-FLICE**-1 or **I-FLICE**-2 activity. Also provided are therapeutic methods for treating diseases and disorders associated with apoptosis.

L9 ANSWER 4 OF 4 MEDLINE on STN DUPLICATE 1
97362203. PubMed ID: 9211860. **I-FLICE**, a novel inhibitor of tumor necrosis factor receptor-1- and CD-95-induced apoptosis. Hu S; Vincenz C; **Ni J; Gentz R; Dixit V M.** (Department of Pathology, University of Michigan Medical School, Ann Arbor, Michigan 48109, USA.) Journal of biological chemistry, (1997 Jul 11) 272 (28) 17255-7. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB The pivotal discovery that the death proteases caspase 8 (FLICE) and caspase 10 (Mch4/FLICE2) are recruited to the CD-95 and tumor necrosis factor receptor-1 signaling complexes suggested a mechanism used by these cytotoxic receptors to initiate apoptosis. In this report, we describe the cloning and characterization of **I-FLICE**, a novel inhibitor of tumor necrosis factor receptor-1- and CD-95-induced apoptosis. The overall architecture of **I-FLICE** is strikingly similar to that of FLICE and Mch4/FLICE2. However, **I-FLICE** lacks both a catalytic active site and residues that form the substrate binding pocket, in keeping with its dominant negative inhibitory function. **I-FLICE** is the first example of a catalytically inert caspase that can inhibit apoptosis.

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